The Baylis–Hillman Bromides as Versatile Synthons: A Facile One-Pot Synthesis of Indolizine and Benzofused Indolizine Frameworks

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Abstract: A facile one-pot synthesis of indolizine, benzofused indolizines {pyrrolo[1,2-*a*]quinoline and pyrrolo[1,2-*a*]isoquinoline} derivatives from the Baylis–Hillman (B–H) bromides, via an interesting strategy involving 1,5-cyclization of nitrogen ylides has been described.

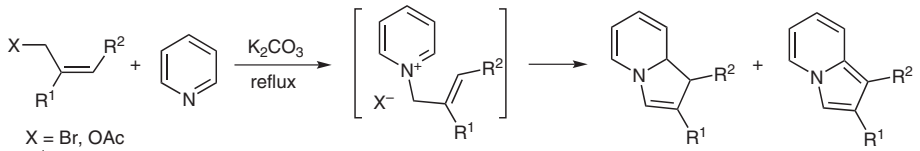
Key words: Baylis–Hillman bromides, 1,5-cyclization strategy, indolizines, benzofused indolizines, quinoline, isoquinoline

Indolizine framework has been and continues to be an interesting and structurally challenging nitrogen heterocyclic moiety because of the presence of this skeleton in a number of bioactive natural products[1,2] such as amorine,[1] erythraline,[1] swainsonine,[1] slaframine,[1] crepidine,[1] gephyrotoxine,[1] cryptaustoline,[2] and cryptowoline.[2] Several indolizine derivatives, in fact, have been known to exhibit various biological activities such as antibacterial activity against mycobacterium tuberculosis,[3a] inhibitors of phosphatase[3b] and aromatase,[3c] antioxidant,[3d] calcium entry blockers,[3e] 5-hydroxytryptamine (5-HT_3) receptor antagonists,[3f] antidepressant,[3g] and antileukemic activities.[3h] The biological and medicinal relevance of the indolizine derivatives has created a need for the development of efficient synthetic strategies for obtaining such derivatives and in fact, several systematic efforts have been made in this direction.[4] In continuation of our ongoing research program in heterocyclic molecules[5] and particularly indolizine framework[6] we herein report a simple and one-pot methodology for obtaining indolizine, benzofused indolizine, pyrrolo[1,2-*a*]quinoline and pyrrolo[1,2-*a*]isoquinoline derivatives using the Baylis–Hillman bromides as synthons.

In recent years the Baylis–Hillman reaction has become one of the most popular carbon–carbon bond-forming reactions in synthetic organic chemistry for obtaining densely functionalized molecules via an efficient atom-economical, one-pot process.[7,8] These densely functionalized molecules, which are commonly referred to as the Baylis–Hillman adducts, have been meticulously and systematically employed in a variety of organic transformation methodologies and also in synthesis of a number of bioactive compounds.[7,8] Efforts were also made for the facile transformation of the Baylis–Hillman adducts into indolizine derivatives.[6,9]

In 1972 Tamura and coworkers reported an elegant conversion of 4-bromo-1,3-diphenylbut-2-en-1-one (involving 1,5-cyclization of nitrogen ylides) into the corresponding indolizine and pyrrolo[1,2-*a*]isoquinoline derivatives via the treatment with pyridine derivatives and isoquinoline, respectively, in the presence of potassium carbonate.[4r] Subsequently, Pohjala reported similar methodology for obtaining dihydroindolizines and indolizine derivatives in high yields. However, in some cases he obtained mixtures of dihydroindolizine and indolizine derivatives (Scheme 1).[4q]

We were indeed fascinated by these wonderful publications.[4q,r] We were particularly pleased to know that allyl bromides used by Pohjala[4q] were equivalent to the present-day Baylis–Hillman bromides (they were not known at that time with this name). It subsequently occurred to us that this strategy would constitute a basis for the preparation of various indolizine and benzofused indolizine {pyrrolo[1,2-*a*]quinoline and pyrrolo[1,2-*a*]isoquinoline} frameworks using the B–H bromides (derived from 2-methylene-3-hydroxy-3-arylpropanenitriles which in turn can be easily prepared via the B–H coupling of acrylonitrile with aryl aldehydes)[8z] as shown in the retrosynthetic scheme involving a 1,5-cyclization strategy (Scheme 2).



X = Br, OAc
R^1 = H, Ac, Ph, PhCO
R^2 = H, Ph, PhCO, 4-$MeOC_6H_4$

Scheme 1

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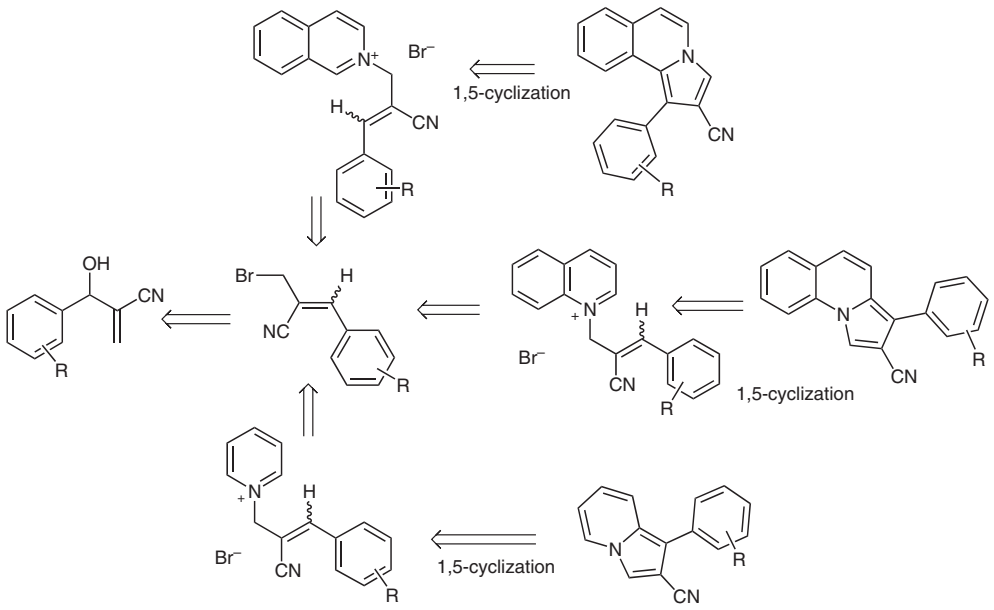


Scheme 2 Retrosynthetic strategy for the synthesis of indolizine and benzofused indolizine derivatives

Accordingly, we first directed our studies towards the transformation of 2-(bromomethyl)-3-phenylprop-2-enenitrile (**1a**, as a mixture of *E*- and *Z*-isomers,[10] the Baylis–Hillman bromide derived from 3-hydroxy-3-phenyl-2-methylenepropanenitrile, which in turn was prepared via the B–H reaction between benzaldehyde and acrylonitrile) into indolizine {1-aza-8-cyano-7-phenylbicyclo-[4.3.0]nona-2,4,6,8-tetraene} **2a** via the treatment with pyridine. The best results in this approach were obtained when 2-(bromomethyl)-3-phenylprop-2-enenitrile (**1a**) was treated with pyridine for 15 minutes at room temperature (for salt formation), followed by heating at 80 °C in the presence of potassium carbonate for three hours, thus providing the desired 1-aza-8-cyano-7-phenylbicyclo-[4.3.0]nona-2,4,6,8-tetraene (**2a**)[11] in 52% isolated yield after purification through column chromatography (Table 1). We have also obtained single crystals for the compound **2a** and further confirmed the structure by single-crystal X-ray data (see Figure 1 for the ORTEP representation).[12]

Encouraged by these results, we successfully transformed representative Baylis–Hillman bromides **1b–j** into the desired 1-aza-8-cyano-7-arylbicyclo[4.3.0]nona-2,4,6,8-tetraenes **2b–j** in 47–63% yields (Table 1). After developing a simple one-pot methodology for the synthesis of indolizine framework we have directed our attention towards the synthesis of benzofused indolizine {pyrrolo[1,2-*a*]quinoline} derivatives, namely 1-aza-12-cyano-11-aryltricyclo[8.3.0.0^{2,7}]trideca-2,4,6,8,10,12-hexaenes. It appeared to us that this can in principle be achieved via the treatment of the B–H bromides with quinoline. In this case also we have first selected 2-(bromomethyl)-3-phenylprop-2-enenitrile (**1a**) for reaction with quinoline. The best results in this strategy were obtained when the Baylis–Hillman bromide **1a** was treated with quinoline in DMF for one hour at room temperature followed by heating at 80 °C for five hours in the presence of K_2CO_3, thus providing 1-aza-12-cyano-11-phenyltricyclo[8.3.0.0^{2,7}]-trideca-2,4,6,8,10,12-hexaene (**3a**) in 45% isolated yield.[13] We have also confirmed the structure of this molecule by single-crystal X-ray data (see Figure 2 for ORTEP representation).[12,14] In order to understand the generality of this reaction strategy we have subjected various Baylis–Hillman bromides **1b–d**,**f** to the treatment with quinoline under similar conditions to provide 1-aza-12-cyano-11-aryltricyclo [8.3.0.0^{2,7}]tri-deca-2,4,6,8,10,12-hexaenes (pyrrolo[1,2-*a*]quinoline derivatives) **3b–e** in 47–51% isolated yields (Table 2).

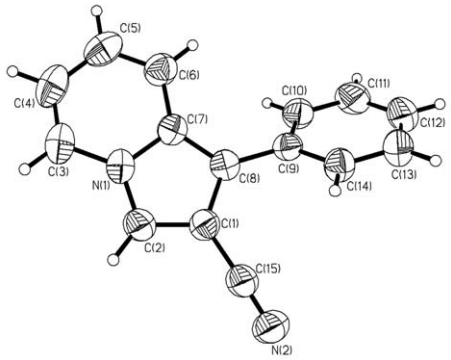
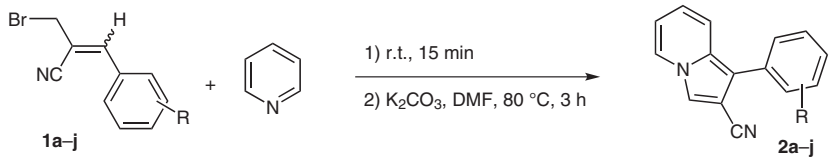


Figure 1 ORTEP diagram of compound **2a**

Next we have focused our attention towards the synthesis of benzofused indolizine {pyrrolo[1,2-*a*]isoquinoline deriveatives} via the treatment of the Baylis–Hillman bromides with isoquinoline. In this case also the best results were obtained when the allyl bromides **1a–d**,**g** were treated with isoquinoline in DMF for one hour at room temperature followed by heating at 80 °C for five hours in the presence of K_2CO_3, thus providing the required benzofused indolizines (1-aza-12-cyano-11-aryltricyclo[8.3.0.0^{4,9}]trideca-

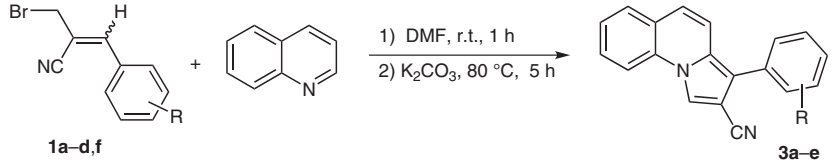
Table 1 Synthesis of Indolizine Derivatives[a]



Entry	B–H bromide	R	Product[b]	Yield (%)[c]
1	**1a**	H	**2a**[d,12]	52
2	**1b**	4-Me	**2b**	54
3	**1c**	4-Et	**2c**	59
4	**1d**	4- *i*-Pr	**2d**	55
5	**1e**	4-NO_2	**2e**	47
6	**1f**	2-Me	**2f**	60
7	**1g**	2-Cl	**2g**	58
8	**1h**	2-Br	**2h**	54
9	**1i**	2,4-$(Cl)_2$	**2i**	63
10	**1j**	3-Cl	**2j**	49

[a] All reactions were carried out on 1 mmol scale of the Baylis–Hillman bromides **1a–j** with pyridine (3 mL).
[b] All the compounds **2a–j** were obtained as colorless solids and fully characterized (see Supporting Information).
[c] Isolated yields of the pure products and based on the B–H bromides.
[d] Structure of this molecule was also established by the single-crystal X-ray data (see Supporting information).[12]

Table 2 Synthesis of Pyrrolo[1,2-*a*]quinoline Derivatives[a]



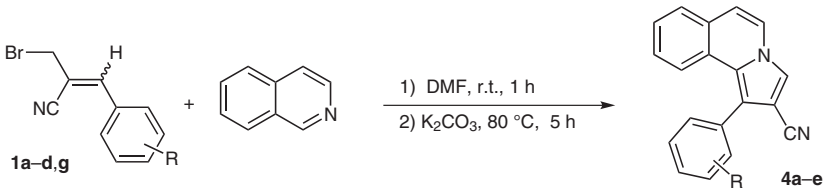
Entry	B–H bromide	R	Product[b]	Yield (%)[c]
1	**1a**	H	**3a**[d,12]	45
2	**1b**	4-Me	**3b**	48
3	**1c**	4-Et	**3c**	47
4	**1d**	4-*i*-Pr	**3d**	51
5	**1f**	2-Me	**3e**	50

[a] All reactions were carried out on 1 mmol scale of the Baylis-–Hillman bromides **1a–d**,**f** with quinoline (2 mmol) in DMF (3 mL).
[b] All the compounds **3a–e** were obtained as colorless solids and fully characterized (see Supporting Information).
[c] Isolated yields of the pure products and based on the B–H bromides.
[d] Structure of this molecule was also established by the single-crystal X-ray data (see Supporting information).[12,14]

2,4,6,8,10,12-hexaenes) **4a–e** in 52–68% isolated yields (Table 3). We have further confirmed the structure of **4a** by single-crystal X-ray data (see Figure 2 for ORTEP representation).[12,14]

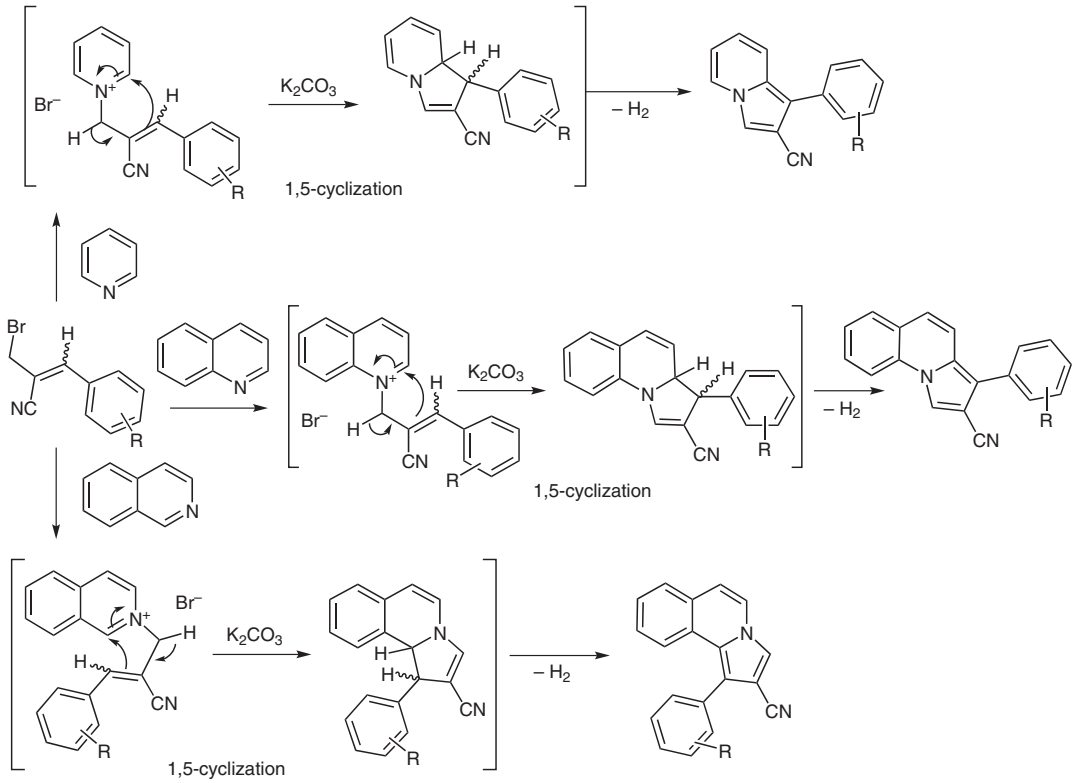
A plausible mechanism (based on 1,5-cylization pathway)[4q,r] for the preparation of indolizine and benzofused indolizine derivatives is provided in the Scheme 3. It is interesting to note that the dihydroindolizine (benzofused dihydroindolizine) derivatives formed in situ underwent dehydrogenation during the course of the reaction to result in the formation of indolizine (benzofused indolizine) frameworks. Although the yields are not very high, this methodology still offers utility in synthesis of pyrrole containing heterocyclic compounds possessing much pharmaceutical relevance.

Table 3 Synthesis of Pyrrolo[1,2-*a*]isoquinoline Derivatives[a]



Entry	B–H bromide	R	Product[b]	Yield (%)[c]
1	**1a**	H	**4a**[d,12]	68
2	**1b**	4-Me	**4b**	63
3	**1c**	4-Et	**4c**	60
4	**1d**	4-*i*-Pr	**4d**	63
5	**1g**	2-Cl	**4e**	52

[a] All reactions were carried out on 1 mmol scale of the Baylis–Hillman bromides **1a–d**,**g** with isoquinoline (2 mmol) in DMF (3 mL).
[b] All the compounds **4a–e** were obtained as colorless solids and fully characterized (see Supporting Information).
[c] Isolated yields of the pure products and based on the B–H bromides.
[d] Structure of this molecule was also established from the single-crystal X-ray data (see Supporting information).[12,14]



Scheme 3 A plausible mechanism for the synthesis of indolizine and benzofused indolizine derivatives

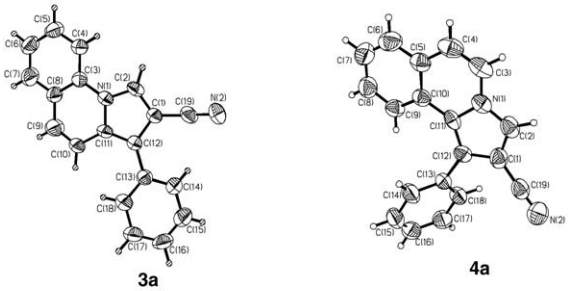


Figure 2 ORTEP diagrams of compounds **3a** and **4a**

In conclusion, we have successfully developed a convenient, facile, and one-pot procedure for the synthesis of indolizine and benzofused indolizine {pyrrolo[1,2-*a*]quinoline and pyrrolo[1,2-*a*]isoquinoline} frameworks from the Baylis–Hillman bromides, thus further demonstrating the applications of Baylis–Hillman bromides as valuable synthons in synthetic organic and medicinal chemistry.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(10) Allyl bromides (as a mixture of *E*- and *Z*-isomers) were prepared by treatment of the Baylis–Hillman alcohols with HBr in the presence of H_2SO_4 following the literature procedure. See: (a) Buchholz, R.; Hoffmann, H. M. R. *Helv. Chim. Acta* **1991**, *74*, 1213. (b) Ameer, F.; Drewes, S. E.; Emslie, N. D.; Kaye, P. T.; Mann, R. L. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2293.

(11) **1-Aza-8-cyano-7-phenylbicyclo[4.3.0]nona-2,4,6,8-tetraene (2a) – Representative Procedure**
To 2-(bromomethyl)-3-phenylprop-2-enenitrile[10] (1 mmol, 0.222 g) pyridine (3 mL) was added and stirred for 15 min (formation of pyridinium salt was observed as shown by TLC) at r.t. The reaction mixture was diluted with DMF (3 mL) and K_2CO_3 (5 mmol, 0.690 g) was added. The reaction mixture was then heated at 80 °C for 3 h and was allowed to cool to r.t. Saturated aq NaCl soln (5 mL) was added and extracted with CH_2Cl_2 (5 × 10 mL). The combined organic layer was dried over anhyd Na_2SO_4. Solvent was evaporated, and the residue, thus obtained, was purified by column chromatography (SiO_2, 5% EtOAc in hexanes) to furnish the pure compound **2a** as a colorless solid. Yield 52% (0.114 g); mp 128–130 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.60–6.70 (m, 1 H), 6.77–6.86 (m, 1 H), 7.32–7.40 (m, 1 H), 7.46–7.53 (m, 2 H), 7.56–7.68 (m, 3 H), 7.74 (s, 1 H), 7.88 (d, 1 H, *J* = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 96.94, 113.60, 116.22, 117.46, 118.16, 118.92, 120.05, 125.31, 127.15, 128.67, 129.00, 129.68, 132.56. IR (KBr): ν = 2222 cm^{-1}. LC-MS: *m/z* = 219 [M + H]$^+$. Anal. Calcd for $C_{15}H_{10}N_2$: C, 82.55; H, 4.62; N, 12.84. Found: C, 82.51; H, 4.65; N, 12.70.

(12) Detailed X-ray crystallographic data are available from the CCDC, 12 Union road, Cambridge CB2 1EZ, UK; for compounds **2a** (CCDC # 693505), **3a** (CCDC # 693506), **4a** (CCDC # 693507).

(13) **1-Aza-12-cyano-11-phenyltricyclo[8.3.0.0^{2,7}]trideca-2,4,-6,8,10,12-hexaene (3a) – Representative Procedure**
To a stirred solution of 2-(bromomethyl)-3-phenylprop-2-enenitrile (1 mmol, 0.222 g) in DMF (3 mL) was added quinoline (2 mmol, 0.258 g) at r.t. After stirring for 1 h (salt formation was observed as evidenced by TLC), K_2CO_3 (5 mmol, 0.690 g) was added and heated for 5 h at 80 °C. The reaction mixture was allowed to cool to r.t. and diluted with sat. aq NaCl soln (5 mL) and extracted with CH_2Cl_2 (5 × 10 mL). The combined organic layers were dried over anhyd Na_2SO_4. Solvent was evaporated, and the residue, thus obtained, was purified by column chromatography (SiO_2, 8% EtOAc in hexanes) to furnish the pure compound **3a** as a colorless solid. Yield 45% (0.120 g); mp 160–162 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.11 (d, 1 H, *J* = 9.6 Hz), 7.34–7.68 (m, 9 H), 7.85 (d, 1 H, *J* = 8.4 Hz), 8.26 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 96.68, 114.43, 116.19, 117.35, 118.04, 120.39, 122.03, 124.52, 125.64, 127.50, 128.10, 128.84, 128.92, 129.00, 129.05, 132.28, 132.38. IR (KBr): ν = 2226 cm^{-1}. LC-MS: *m/z* = 269 [M + H]$^+$. Anal. Calcd for $C_{19}H_{12}N_2$: C, 85.05; H, 4.51; N, 10.44. Found: C, 85.11; H, 4.54; N, 10.57.

(14) The single crystal X-ray structure revealed the presence of two molecules in the asymmetric unit. For clarity we have shown one molecule in the ORTEP diagram.